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SYNTHESIS AND ANTI-HIV ACTIVITY OF L-2'-FLUORO-2',3'-UNSATURATED PURINE NUCLEOSIDES

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Abstract: *The synthesis of 9-(2,3-dideoxy-2-fluoro-L-glycero-pent-2-eno-furanosyl)adenine and -hypoxanthine has been accomplished by direct condensation of silylated 6-chloropurine with key intermediates 8, which were prepared starting from 2,3-O-isopropylidene-L-glyceraldehyde. The synthesized nucleosides were evaluated against HIV-1 in vitro in primary human lymphocytes (PMB cells). It was found that β-L-Fd4A 12 exhibited moderately potent anti-HIV activity (EC_{50} 1.5 μM).*

The intense efforts in the search for more effective and less toxic antiviral agents against the human immunodeficiency virus (HIV) and hepatitis B virus (HBV) have led to the discovery of 2',3'-dideoxy nucleoside analogs, such as AZT,[1] ddC,[2] ddI,[3] and d4T[4] and unnatural L-nucleoside analogs, such as 3TC,[5] FTC,[6] and L-FMAU[7]. Recently, we have reported the synthesis and antiviral activity of β-L-2',3'-dideoxy (β-L-d2N)- and 2',3'-didehydro-2',3'-dideoxy (β-L-d4N)-purine nucleosides, among which β-L-d4A exhibited the most potent antiviral activity against HIV.[8] However, it has been well known that d2- and d4-purine nucleosides are unstable in acidic media, resulting in glycosyl bond cleavage, thus limiting their use as orally bioavailable drugs.[9] Introduction of a fluorine atom at the 2'-position in those dideoxypurine nucleosides is known to stabilize the glycosyl bond[10, 11] and, moreover, a variety of fluorinated compounds have been shown to exhibit broad biological activities.[11] Therefore, it was of interest to sythesize d4N with a fluorine atom at the 2'-position, which could result in significant biological activity and the stabilization of glycosyl bond. Herein, we describe the synthesis of purine nucleosides containing vinylic fluorine and their anti-HIV activity.

Previously, the synthesis of 2',3'-unsaturated D-nucleosides was achieved *via* elimination reactions starting from readily available nucleoside analogs. This involved a lengthy modification for individual nucleosides. Several groups reported the preparation of D-2'-fluoro-2',3'-unsaturated pyrimidine nucleosides by the elimination of suitable 2'-fluorinated nucleoside analogs.[12] This strategy for the synthesis of L-Fd4N, however, is accompanied by additional difficulties in the use of L-nucleosides as the starting material. There are few examples for the synthesis of 2',3'-unsaturated purine nucleosides by the direct condensation due to the lability of the 2,3-unsaturated sugar moiety under the coupling conditions in the presence of Lewis acid, except one case for the pyrimidine analogs using a thiophenyl intermediate.[13] In contrast to the 2,3-unsaturated sugar moiety, the 2-fluoro-2,3-unsaturated sugar bears enhanced stability of the glycosyl bond during its condensation with a heterocycle and was expected to be more suitable for the direct coupling reaction. Thus, (*R*)-2-fluorobutenolide **6**, as a precusor for the key intermediates **8**, was chosen and prepared from 2,3-*O*-isopropylidene-L-glyceraldehyde (**Scheme 1**).

Starting from 2,3-*O*-isopropylidene-L-glyceraldehyde (**1**), a mixture of (*E*)-**2**/(*Z*)-**2** (9:1 by ^{1}H NMR) was

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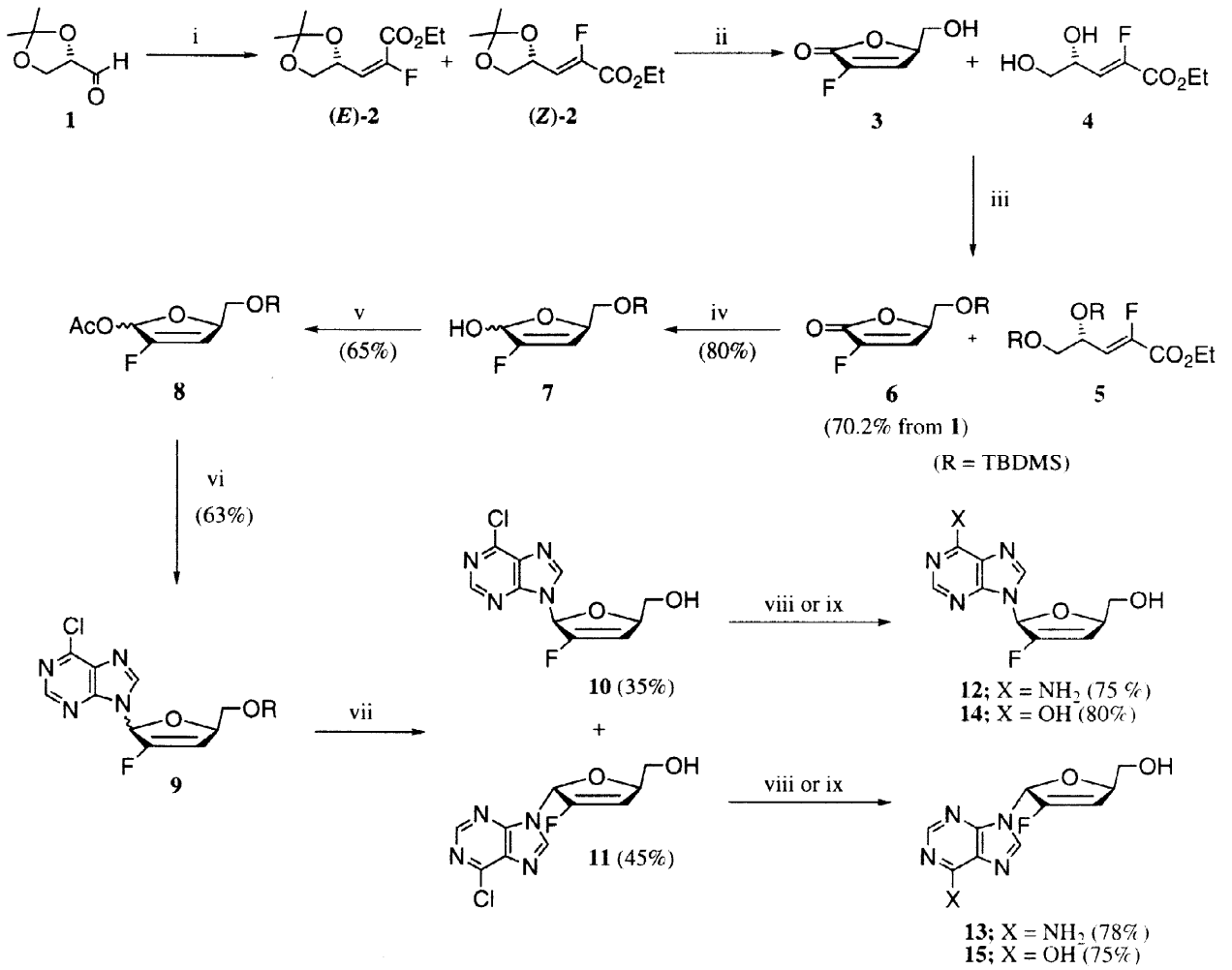
Scheme 1. Synthesis of L-2'-Fluoro-d4Adenine and -Hypoxanthine by Direct Condensation



Reagents: (i) $(EtO)_2P(O)CHFCO_2Et$, $[(CH_3)_3Si]_2NNa$, THF, -78 °C (ii) HCl/EtOH (iii) TBDMSCl, imidazole, CH_2Cl_2 (iv) 1 M DIBAL-H in CH_2Cl_2, CH_2Cl_2, -78 °C (v) Ac_2O, pyr., CH_2Cl_2 (vi) silylated 6-Cl-purine, TMSOTf, DCE (vii) TBAF, CH_3CN (viii) NH_3/MeOH, 90 °C (ix) $HS(CH_2)_2OH$, NaOMe/MeOH, reflux

Table 1. Median Effective (EC_{50}) and Inhibitory (IC_{50}) Concentration of L-2'-Fluoro-d4Adenine and Hypoxanthine against HIV-1 in human PBM cells

Compound No.	EC_{50} (μM) (PBM Cells)	EC_{90} (μM) (PBM Cells)	Cytotoxicity		
			PBM Cells	Vero Cells	CEM Cells
			IC_{50} (μM)	IC_{50} (μM)	IC_{50} (μM)
12	1.5	15.1	> 100	> 100	> 100
13	47.6	332	> 100	> 100	> 100
14	> 100	> 100	> 100	> 100	> 100
15	> 100	> 100	> 100	> 100	> 100
AZT	0.004	0.04	> 100	29.0	14.3

obtained *via* the Horner-Emmons reaction in the presence of triethyl α-fluorophosphonoacetate and sodium bis(trimethylsilyl) amide in THF.[14] Due to the difficulties in separating the (*E*)-**2**/(*Z*)-**2** isomers, the mixture was used in the following cyclization reaction under acidic condition to give the desired lactone **3** and uncyclized diol **4**. The resulting mixture was converted to the corresponding silyl derivatives, which were readily separated to give **5** and **6** (70.2% yield from compound **1**). The silylated lactone **6** was subjected to reduction with DIBAL-H in CH_2Cl_2 at -78 °C to give a mixture of lactols **7**. The lactols **7** were treated with acetic anhydride to yield the key intermediates **8**, which were condensed with silylated 6-chloropurine under Vorbrüggen conditions to afford anomeric isomers **9**. Treatment of **9** with TBAF in THF gave free nucleosides **10** and **11**, which were readily separated by silica gel column chromatography. Adenine analogs **12**[15] and **13**[16] were obtained by the treatment of compound **10** and **11** in methanolic ammonia in a steel bomb at 90 °C, respectively. Treatment of compound **10** and **11** with mercaptoethanol and NaOMe afforded the inosine analogs **14**[17] and **15**,[18] respectively. The stereochemical assignment of these compounds was based on the NOESY spectroscopy (cross peak between H-1' and H-4' in β-isomer **12**).

In conclusion, we accomplished the direct condensation of a 2,3-unsaturated sugar moiety with a silylated purine base in an efficient manner. The synthesized nucleoside **12** exhibited moderately potent anti-HIV activity (**Table 1**). The synthesis of other purine and pyrimidine nucleosides is in progress and will be reported shortly.

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15. **9-(2,3-Dideoxy-2-fluoro-β-L-glycero-pent-2-enofuranosyl)adenine (12):** mp 188-190 °C; $[\alpha]^{26}_D$ = -54.9 (c 0.17, MeOH); UV (H_2O) λ_{max} 258 nm (ε 18,800) (pH 2), 258.5 nm (ε 18,800) (pH 7), 258.5 nm (ε 19,100) (pH 11); ^{1}H NMR (DMSO-*d*) δ 3.63 (s, H-5'), 4.91 (s, H-4'), 6.08 (s, H-3'), 6.90 (s, H-1'), 8.17 (s, H-2), 8.40 (s, H-8); ^{13}C NMR (DMSO-*d*) δ 65.06, 83.74, 85.62, 109.28, 121.17, 141.65, 151.79, 152.76, 155.40, 158.57; Anal. Calcd for $C_{10}H_{10}FN_5O_2 \cdot 0.2H_2O$: C, 47.13; H, 4.11; N, 27.48. Found: C, 47.02; H, 4.13; N, 27.26.
16. **9-(2,3-Dideoxy-2-fluoro-α-L-glycero-pent-2-enofuranosyl)adenine (13):** mp 168-171 °C; $[\alpha]^{26}_D$ = +160.6 (c 0.19, MeOH); UV (H_2O) λ_{max} 258 nm (ε 21,100) (pH 2), 259 nm (ε 21,500) (pH 7), 259 nm (ε 22,600) (pH 11); ^{1}H NMR (DMSO-*d*) δ 3.57 (m, H-5'), 5.14 (ps t, J = 3.9, 4.3 Hz, H-4'), 6.06 (s, H-3'), 6.89 (ps t, J = 3.9, 4.1 Hz, H-1'), 8.17 (s, H-2), 8.31 (s, H-8); ^{13}C NMR (DMSO-*d*) δ 62.92, 81.88, 83.44, 106.99, 118.89, 139.03, 149.12, 150.27, 152.99, 155.95; Anal. Calcd for $C_{10}H_{10}FN_5O_2 \cdot 0.3$MeOH: C, 47.33; H, 4.33; N, 26.85. Found: C, 47.42; H, 4.23; N, 26.91.
17. **9-(2,3-Dideoxy-2-fluoro-β-L-glycero-pent-2-enofuranosyl)hypoxanthine (14):** mp 128-130 °C; $[\alpha]^{24}_D$ = -50.2 (c 0.2, MeOH); UV (H_2O) λ_{max} 247 nm (ε 12,400) (pH 2), 247.5 nm (ε 13,000) (pH 7), 253 nm (ε 13,100) (pH 11); ^{1}H NMR (DMSO-*d*) δ 3.67 (s, H-5'), 4.98 (s, H-4'), 6.15 (ps t, J = 1.6 Hz, H-3'), 6.94 (m, H-1'), 8.17 (s, H-2), 8.43 (s, H-8); ^{13}C NMR (DMSO-*d*) δ 65.97, 84.87, 86.94, 110.62, 127.64, 142.00, 149.93, 151.74, 153.56, 159.97; Anal. Calcd for $C_{10}H_9FN_4O_3 \cdot 0.2$MeOH: C, 47.37; H, 3.82; N, 21.66. Found: C, 47.11; H, 3.77; N, 21.50.
18. **9-(2,3-Dideoxy-2-fluoro-α-L-glycero-pent-2-enofuranosyl)hypoxanthine (15):** mp 200 °C (dec.); $[\alpha]^{26}_D$ = +157.3 (c 0.22, MeOH); UV (H_2O) λ_{max} 247.5 nm (ε 12,700) (pH 2), 247.5 nm (ε 13,700) (pH 7), 252.5 nm (ε 13,100) (pH 11); ^{1}H NMR (DMSO-*d*) δ 3.56 (m, H-5'), 5.13 (ps t, J = 3.6, 3.7 Hz, H-4'), 6.06 (s, H-3'), 6.87 (ps t, J = 2.7, 5.3 Hz, H-1'), 8.09 (s, H-2), 8.26 (s, H-8); ^{13}C NMR (DMSO-*d*) δ 63.39, 82.88, 84.24, 107.84, 125.13, 139.20, 146.84, 148.59, 150.75, 156.92; Anal. Calcd for $C_{10}H_9FN_4O_3 \cdot 0.3H_2O$: C, 46.62; H, 3.76; N, 21.75. Found: C, 46.86; H, 3.80; N, 21.56.